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Effect of celecoxib on benign prostatic hyperplasia: Results of a preliminary study

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ABSTRACT

Objective: Today, the role of inflammation in the pathophysiology of benign prostatic hyperplasia (BPH) has become quite evident. Numerous markers have been found which suggests a role of non-bacterial inflammation in the prostate. Despite the recommendation of anti-inflammatory drugs for BPH, research on the effectiveness of such drugs is scant. Hence, the present study examined the effectiveness of celecoxib in treating patients with BPH.

Materials and Methods: This single-blind randomized control trial was conducted on 160 patients referred to a urology clinic from 2006 to 2007. Patients were aged ≥50 years, had obstructive and irritative symptoms of BPH, and had American Urological Association (AUA) scores ranging 7–25. They were randomly assigned to control (treated with 2 mg terazosin) and celecoxib (2 mg terazosin with 200 mg celecoxib) groups and underwent 12 weeks of treatment.

Results: The baseline measures for the severity of symptoms, postvoiding residual urine (PVR), prostate volume, and prostate-specific antigen (PSA) level did not significantly differ between the two groups. The severity of symptoms and PVR significantly decreased after treatment in both groups. However, the prostate volume and PSA level significantly dropped as well in the celecoxib group. The overall severity of symptoms, irritative symptoms, and prostate volume decreased more in the celecoxib group than in the control group.

Conclusion: The present study showed that combination therapy with celecoxib and terazosin can significantly decrease irritative symptoms of BPH and prostate volume as well. Therefore, it seems that adding anti-inflammatory drugs to routine treatment for BPH could be more effective than routine therapy.

1. Introduction

Benign prostatic hyperplasia (BPH) is a pathological condition of the prostate that mainly involves the central zone of the prostate gland.[1] From a histological view, this condition is observed in 8% of autopsies in men in the third decade of their lives. The prevalence of this condition increases as men age and reaches 50%, 70%, and 90% in the fifth, seventh, and eighth decades of life, respectively.[2] However, a study conducted in the US showed that moderate to severe urinary symptoms of BPH begin to appear in the third decade in patients, and its clinical prevalence increases to 45% and 62% in the fifth and seventh decades of life, respectively.[3] Despite not being a life-threatening problem, BPH can affect the quality of life in various ways. In fact, patients with lower urinary tract symptoms (LUTSs) suffer from various problems in terms of sleep, daily mobility, household chores, recreational activities, and sexual relationships.[4,5] Nevertheless, only a small percentage of these patients receive proper diagnosis and treatment.[5]

There are different treatment options for BPH patients. In cases of mild to moderate severity which do not result in inconvenience, watchful waiting treatment is preferred. For patients with more severe symptoms, surgical or medical treatment may be used according to the patient's performance and preferences. Today, the use of α_1-adrenergic-receptor antagonists and 5α-reductase inhibitors has reduced the tendency for surgery and decreased side effects, such as retrograde ejaculation, impotence, urinary incontinence, hemorrhage, stricture of the urethra, constriction of the bladder neck, perforation of the prostatic capsule, and urinary tract infections.[6–8] α_1-Adrenergic receptor antagonists release the smooth muscle tone of the prostate gland and the urethra and are therefore chosen as an effective medication for BPH because of

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their immediate effect, relative safety, and proven efficacy. However, these drugs do not result in a change in the prostate size.[9,10] 5α-Reductase inhibitors are effective through another mechanism which causes shrinkage of the prostate via inhibiting the enzyme converting testosterone to dihydrotestosterone.[11] A combination of these two drugs was examined in several clinical trials proving their relative superior effectiveness over any monotherapy.[12–15] However, dizziness, asthenia, nasal congestion, orthostatic hypotension, impotence, and ejaculation disorders are common side effects associated with these drugs[15] which may be problematic if patients also have senile conditions, such as cardiovascular disease, hypertension, diabetes, metabolic syndrome, and sexual disorders.[2]

The role of inflammation in the pathophysiology of BPH has been highlighted in recent years, and various markers were found to verify the non-bacterial nature of inflammation in the prostate.[16] In fact, some studies recognized chronic inflammation of the prostate as underlying prostatic hyperplasia and certain urinary symptoms.[17] In another study, the effects of inflammatory severity in pathologic samples obtained through transrectal ultrasonography (TRUS)-guided needle biopsy on the symptoms and quality of life were investigated. They found that a drop in the severity of symptoms and an increase in the quality of life occurred faster and were sustained longer in patients with a lesser extent of inflammation compared to those with more severe inflammation.[18] Thus, medical treatment of prostatic inflammation as part of BPH treatment is commonly recommended.[18] Despite the recommendation of anti-inflammatory drugs for BPH, research on the effectiveness of such drugs is scant. Since prostaglandins are key factors in the development of inflammation, cellular invasion, apoptosis, angiogenesis, and balancing immunological reactions, it seems that cyclooxygenase (COX)-2 inhibitors may effectively contribute to decreased inflammation of prostatic tissues in BPH and significantly reduce symptoms and the prostatic volume. This postulation is based on the COX-2 enzyme playing an important role in the synthesis of prostaglandins. Celecoxib is a selective inhibitor of this enzyme which was shown to reduce nocturia in BPH patients.[19] The present study therefore examined the effect of celecoxib as a supplementary medication for BPH on urinary symptoms, postvoiding residual urine (PVR), prostatic volume, and the PSA level.

2. Materials and methods

2.1. Patient selection

This single-blind randomized control trial was conducted on patients seeking treatment at the Urology Clinic of Vali Asr Hospital, Arak, Iran in the period of January 2006 to April 2007. Patients aged ≥50 years with irritative and obstructive symptoms of BPH were selected. They also had to meet the following inclusion criteria: the presence of obstructive-irritative symptoms caused by BPH; a score of 7–25 on the American Urological Association (AUA) symptom scale (equal to moderate symptoms); prostatic hyperplasia without induration, nodules, or asymmetry on a digital rectal examination (DRE); unlikely to be afflicted with other causes of LUTSs, such as urinary tract infection, neurogenic bladder, or urethral constriction based on history taking, clinical examination, sonography, and laboratory tests; no presence of indications for prostate surgery, including severe life-threatening symptoms, persistent urinary retention (failure to discharge without a catheter with more than one attempt), recurrent urinary tract infection due to BPH, severe recurrent hematuria, renal failure (high levels of blood urea nitrogen (BUN) and creatine (Cr)) due to BPH, and bladder stones caused by BPH; no presence of abnormal PSA, large bladder diverticula, or gastrointestinal problems, such as peptic ulcer; and a lack of history of sensitivity to the treatment drugs (terazosin and celecoxib).

Satisfaction of the inclusion criteria was confirmed by a urologist and verified through digital rectal examination, urine analysis (UA) and culture (UC), AUA symptom score, and laboratory tests (PSA, BUN, and Cr). Patients were briefed about the goals of the study and the likely side effects of the treatment drugs. Informed consent was obtained from all patients as well. The present study was conducted in compliance with ethical statements 1 and 2 of the *Helsinki Declaration* and all 26 ethical statements established by the Iranian Ministry of Health. In addition, ethical approval was also received from the ethics committee of Arak University of Medical Sciences. Two hundred patients meeting the entry requirements were randomly assigned to the control and celecoxib groups. However, 40 patients dropped out, and 160 patients (80 in each group) remained to the end of the treatment for data analysis. Among those 40 patients, 12 patients in the control group and 10 patients in the celecoxib group failed to follow-up their treatment. In addition, eight and 10 patients in the control and celecoxib groups, respectively, refused to reevaluate their PSA and sonography.

2.2. Intervention

The control group received terazosin alone (2 mg as a single dose at night), and the celecoxib group received combination therapy of terazosin (2 mg as a single dose at night) and celecoxib (200 mg every 12 hours) for 12 weeks. Terazosin, in the form of a 2-mg tablet, and celecoxib, in the form of a 200-mg capsule, were supplied by the Hakim Pharmaceutical Co., Tehran, Iran and the Darou Pakhsh Pharmaceutical Co. Tehran, Iran, respectively. In order to prevent hemodynamic effects of terazosin, it was titrated for both groups in a 1-mg (half tablet) dosage before sleep in the first 2 days and 2 mg (full tablet) for the remaining treatment. In the celecoxib group, however, celecoxib was prescribed twice a day to be taken along with daily meals.

2.3. Measures

In addition to the foregoing inclusion criteria, the ages of participants were recorded. A sonography specialist conducted bladder and prostate sonography to measure the PVR and prostrate volume. Transrectal sonography used an SIUI CTS 200 Ultrasound System (Shantou Institute of Ultrasonic Instruments Co., Guangdong, China). The prostrate volume was calculated by two circular or ellipsoidal perpendicular planes according to the prostate shape. Symptom severity of BPH was measured using the AUA symptom score by an assistant who was blinded to the individual patient's group. The AUA questionnaire measures seven obstructive and irritative symptoms of BPH, including incomplete emptying, urination frequency, intermittency, urgency, a weak stream, straining, and nocturia in the past month. A measure of each symptom is taken on a 6-point scale, ranging from 0 to 5. The overall severity is calculated by the addition of individual measures, ranging from 0 to 35, in which a higher score indicates more severe symptoms. The severity of irritative symptoms was calculated by adding up individual scores from urination frequency, urgency, and nocturia. Adding individual scores of the rest of the measures produced an obstructive symptoms severity score.[10] Patients were visited monthly to evaluate clinical progression, drug compliance, and side effects during the study period. Sonography reevaluation was conducted at the end of treatment in order to assess the PVR and prostate volume. The PSA value and AUA questionnaire were also re-assessed. Side effects, including hemodynamic conditions (orthostatic hypotension, fatigue, dizziness and palpitation) and gastric problems were also recorded.

Table 1
Comparison of the mean (±standard deviation) of symptoms severity, postvoiding residual urine, prostate volume and prostate-specific antigen (PSA) within and between groups.

	Control group ($N = 80$)			Celecoxib group ($N = 80$)			Between-group comparison (p^b)	
	Pre	Post	p^a	Pre	Post	p^a	Pre	Post
AUA symptoms score	17.0 ± 5.7	10.3 ± 4.2	**<0.001**	16.9 ± 6.1	7.7 ± 4.1	**<0.001**	0.937	**<0.001**
Obstructive symptoms severity	9.4 ± 4.2	4.8 ± 2.9	**<0.001**	9.2 ± 4.4	4.0 ± 2.9	**<0.001**	0.785	0.067
Irritative symptoms severity	7.6 ± 2.4	5.4 ± 2.1	**<0.001**	7.7 ± 3.2	3.4 ± 2.3	**<0.001**	0.800	**<0.001**
Postvoiding residual urine (mL)	38.5 ± 29.9	22.7 ± 19.5	**<0.001**	35.6 ± 30.4	20.1 ± 18.6	**<0.001**	0.547	0.389
Prostate volume (mL)	43.4 ± 18.9	43.0 ± 17.2	0.454	44.0 ± 19.3	38.3 ± 16.8	**<0.001**	0.840	0.081
PSA (ng/mL)	3.54 ± 3.58	3.17 ± 1.66	0.238	3.36 ± 2.39	2.77 ± 1.74	**0.013**	0.709	0.143

Note. Statistically significant p values between groups are indicated in bold font.
[a] paired t test
[b] independent sample t test.

2.4. Statistical analysis

SPSS 16.0 for Windows (SPSS, Chicago, IL, USA) was used to perform the required statistical analyses. Data were described using the mean and standard deviation. An independent t test was used to measure variations in age, overall severity of symptoms, severity of obstructive and irritative symptoms, the PVR, prostate volume, and PSA level before and after the intervention in the two groups. To compare changes in these variables after the intervention in each group, a paired t test was used. A p value of <0.05 was considered significant.

3. Results

The range and mean age ± standard deviation of patients were 50–85 and 66 ± 9 years, respectively. The two groups did not significantly differ in the age variable ($p = 0.852$). Table 1 presents the baseline measures for the severity of symptoms, PVR, prostate volume, and PSA levels for these two groups. There was no significant difference between the two groups. The 12-week treatment in the celecoxib group significantly decreased all measures compared to the baseline. However, in the control group, the prostate volume and PSA level did not significantly decrease (Table 1). In addition, the amounts of the decrease in the overall severity of symptoms and irritative symptoms scores in the celecoxib group were greater than those of the control group (Table 2).

The hemodynamic side effects associated with terazosin (orthostatic hypotension, fatigue, dizziness, and palpitations) were detected in 12 participants from both groups (15%). Gastric problems were reported by eight (10%) and 12 patients (15%) in the control and celecoxib groups, respectively. However, the side effects were not severe enough to interrupt the treatment.

4. Discussion

The findings in the present study show that 3-month supplementary treatment with celecoxib and terazosin in BPH patients significantly reduced the overall severity of urinary symptoms, individual obstructive and irritative symptoms, PVR, prostate volume, and PSA level. However, compared to terazosin-alone treatment, greater decreases were achieved in the overall severity of symptoms, severity of irritative symptoms, and prostate volume.

Table 2
The mean (±standard deviation) of decreases in symptoms severity, postvoiding residual urine, prostate volume, and prostate-specific antigen (PSA).

	Control group ($N = 80$)	Celecoxib group ($N = 80$)	p^a
AUA symptoms score	(−6.7) ± 5.7	(−9.2) ± 6.9	**0.014**
Obstructive symptoms severity	(−4.5) ± 3.9	(−5.2) ± 5.1	0.369
Irritative symptoms severity	(−2.2) ± 2.7	(−4.3) ± 3.6	**<0.001**
Postvoiding residual urine (mL)	(−15.8) ± 21.6	(−15.6) ± 21.7	0.393
Prostate volume (mL)	(−0.4) ± 4.8	(−5.7) ± 7.0	**<0.001**
PSA (ng/mL)	(−0.38) ± 2.9	(−0.59) ± 2.1	0.585

Note. Statistically significant p values between groups are indicated in bold font.
[a] independent sample t test.

The role of chronic inflammation was considered in many studies. Nickel et al[20] in 2008 found that 77.6% of patients with LUTSs suffered from chronic inflammation, and the degree of chronic inflammation corresponded to the severity of symptoms. Furthermore, advanced prostate hyperplasia and acute urinary retention caused by chronic and symptom-free inflammation of the prostate were also reported.[21–23] In addition, Chuang et al[24] also showed higher serum C-reactive protein (CRP) levels, a widely used marker of inflammation and infection, in BPH patients compared to asymptomatic controls. So, anti-inflammatory treatment for BPH is reccomended.[25] However, little research has been conducted to verify the effect of anti-inflammatory agents on BPH. Falahatkar et al[19] showed that celecoxib treatment can decrease or eliminate nocturia in more than 80% of participants. Di Silverio et al[26] also showed that rofecoxib (another COX-2 inhibitor) was able to improve the clinical signs of BPH patients before the emergence of clinical effects of finastride. In addition, studies using diclofenac and indomethacin also showed a decrease in nocturia.[27,28] The results of our study also showed a better response with celecoxib/terazosin combination treatment than terazosin alone in decreasing symptoms, particularly irritative ones, and leading to a decrease in prostate volume as well. As it is known that chronic inflammation of the prostate is related to the higher volume of this gland[20] and terazosin-alone treatment did not result in a reduction in the prostate volume,[29] we may attribute the reduction in the prostate volume to a decrease in chronic inflammation of the gland by celecoxib.

Various studies showed the expression of COX-2 in prostatic cells of both BPH and prostatic cancer patients.[30–32] Expression of this isoenzyme in luminal epithelial cells within ducts adjacent to foci of chronic inflammation, which was shown by Wang et al,[33] led to a higher proliferation rate and upregulated the antiapoptotic gene, Bcl-2. Enhanced expression of this gene can deregulate normal apoptotic cell death mechanisms resulting in imbalanced growth of prostatic tissue.[34–36] So this could be one of the mechanisms by which COX-2 inhibitors reduced the prostate volume in our study. In addition, prostaglandins also play a special role in urine production.[37] Therefore, other effective mechanisms of this drug in treating LUTSs may be a reduction in urine production by the kidneys, reduction of inflammation of prostatic tissue, and an indirect effect of these factors on patients' sleep quality through a reduction in nocturnal symptoms.[19] Furthermore, celecoxib causes atrophy and reduction of Leydig cells, which in turn reduces the prostate volume by decreased production of testosterone.[38]

Since celecoxib only inhibits COX-2, without any effect on COX-1 (which when inhibited causes several side effects, such as gastric

ulcers and hemorrhage, renal dysfunction, and inhibition of platelet aggregation), it causes few gastric, renal, or hemorrhagic problems.[39] Our study also showed few side effects of this drug, which were too weak to discontinue treatment. Di Silverio et al[28] likewise reported few and weak side effects. Our preliminary study generally showed that COX-2 inhibitors are well tolerated by patients and are able to reduce symptoms and prostate volume associated with BPH.

The problem of distinguishing between chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) and LUTSs of BPH is an important point in the interpretation of our results. However, according to the greater age of our patients, normal UA and UC exams, and confirmation of BPH by a urologic examination, it seems that almost all of our patients suffered from BPH not CPPS. Another point is that we had no run-in period for excluding noncompliant subjects, placebo responders, or subjects who could not tolerate or did not respond to the active drugs, but taking into account the clear evidence indicating a prostatic inflammatory process in BPH patients and heeding the recommendation for the use of anti-inflammatory drugs, it seems that celecoxib may be effective for this purpose. Therefore, further research with a larger sample size, using a run-in period, using other COX-2 inhibitors, using a placebo group, and if possible, measuring the effect of COX-2 inhibitor treatment on changes in inflammatory biomarkers is needed in order to examine the precise effect of this group of drugs on BPH patients and their mechanisms, identify the appropriate dosage and treatment duration.

5. Conclusion

The present study showed that celecoxib/terazosin combination therapy in BPH patients can reduce the severity of symptoms in general and irritative ones in particular more than single therapy with terazosin, and it can also decrease the prostate volume. Therefore, since prostatic inflammation in BPH is confirmed, it seems that prescribing anti-inflammatory drugs for these patients may prove effective. Therefore, further research with a larger sample size and use of various COX-2 inhibitors alongside a placebo group is highly encouraged in order to conduct more-precise studies on the effectiveness of these anti-inflammatory drugs in BPH.

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